Severe adverse events during antiviral therapy in hepatitis C virus cirrhotic patients: a systematic review
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CRD summary
The review concluded that 14.5% of cirrhotic patients infected with hepatitis C virus treated with pegylated interferon and ribavirin needed early discontinuation of therapy due to severe adverse events. Differences between the included studies and a lack of quality assessment mean that the authors' conclusions may not reflect the proportion of patients requiring early discontinuation in practice.

Authors' objectives
To investigate the severe adverse events that lead to treatment discontinuation during treatment with pegylated interferon and ribavirin antiviral therapy in cirrhotic patients infected with hepatitis C virus.

Searching
PubMed, MEDLINE, LILACS, Scopus, EMBASE, The Cochrane Library and Medscape databases were searched up to December 2011 for studies in English; search terms were reported.

Study selection
Eligible studies assessed the rate of severe adverse events (leading to treatment discontinuation) in cirrhotic patients infected with hepatitis C virus and treated with pegylated interferon alpha 2a (at a dose of 135-180 μg/week) or pegylated interferon alpha 2b (at a dose of 1.0 or 1.5 μg/week) and ribavirin (at a dose of 800 to 1,200 mg/day) were eligible for inclusion. Studies that included liver-transplanted patients or patients co-infected with hepatitis B virus or HIV were excluded from the review.

Where stated, average ages of patients in the included studies ranged from 46 to 57 years and average weights ranged from 71kg to 82kg. Where specified, most studies included patients who had not been previously treated; some studies included both naive and previously treated patients. Patients' hepatitis C virus genotype and Child-Pugh class varied between studies. Patients with hepatitis C virus genotypes 1 and 4 received treatment for 48 weeks; patients with genotypes 2 and 3 received treatment for 24 weeks. Details of antiviral treatment doses were presented in the review.

Two reviewers independently assessed studies for inclusion in the review.

Assessment of study quality
The authors did not state that they assessed study quality.

Data extraction
Data were extracted on rates and descriptions of severe adverse events that lead to treatment discontinuation, the proportion of patients in whom doses of pegylated interferon and/or ribavirin were reduced and the sustained virological response rate according to hepatitis C virus genotype.

The authors did not state how many reviewers extracted these data.

Methods of synthesis
The proportion of patients who discontinued treatment or had dose reductions and the sustained virological response rate (with 95% confidence intervals) were calculated across all of the studies. Standard binomial tests for differences in proportions were used to compare patient subgroups (Child Pugh class, specific type of treatment, hepatitis C virus genotype).

Results of the review
Seventeen prospective and retrospective studies (1,133 patients, range 12 to 106) were included in the review: four randomised controlled trials (279 patients) and 13 cohort studies (854 patients).
Antiviral treatment was stopped early due to severe adverse events in 165 out of 1,133 (14.5%) patients. Where reported (116 patients), the most common severe adverse events that led to premature discontinuation were severe thrombocytopenia and/or neutropenia (23.2%), psychiatric disorders (15.5%), decompensation of liver cirrhosis (12.1%) and severe anaemia (11.2%). The mortality rate was 0.3% (four out of 1,133 patients); causes of death were severe sepsis, decompensation of heart disease, hepatocellular carcinoma and severe hepatic failure.

The rate of severe adverse events leading to antiviral treatment discontinuation was significantly higher in patients with Child-Pugh class B and C than in patients with Child-Pugh class A (22% versus 11.4%; p=0.003; 10 studies). The rate of severe adverse events leading to antiviral treatment discontinuation was similar for pegylated interferon alpha 2a and pegylated interferon alpha 2b (14.2% versus 13.7%). Significantly more patients with hepatitis C virus genotype 1 discontinued antiviral treatment due to severe adverse events than patients with hepatitis C virus genotype 3 (30% versus 8.5%; p=0.02; three studies).

Results were reported on the number of patients in whom doses of pegylated interferon and/or ribavirin were reduced and the sustained virological response rate.

Authors’ conclusions
Fourteen point five per cent of cirrhotic patients infected with hepatitis C virus treated with pegylated interferon and ribavirin needed early discontinuation of therapy due to severe adverse events. The most common type of severe adverse event was haematological disorders.

CRD commentary
The review question and inclusion criteria were clear. Several relevant sources were searched for studies. Language restrictions were applied so some relevant studies may have been missed. Two reviewers independently selected studies for inclusion, which reduced potential for reviewer error and bias; it was not clear whether similar methods were used for data extraction. The authors did not state that they assessed the quality of the included studies, which reduced the reliability of the results.

Many of the included studies had small sample sizes. Differences between studies in patient characteristics, treatment history and treatment doses mean that it may not have been appropriate to combine the results. The subgroup analyses appeared appropriate and demonstrated the significant differences in results according to patient characteristics. No details of treatment-stopping rules for the individual studies were presented so it was unclear whether these varied between studies.

The authors’ conclusions reflect the results of the main analysis but differences in patient characteristics between studies, a lack of details of stopping rules for the individual studies and the lack of a quality assessment mean that the authors' conclusions may not reflect the proportion of cirrhotic patients infected with hepatitis C virus who require early discontinuation of antiviral therapy due to severe adverse events in practice.

Implications of the review for practice and research
The authors did not state any implications for practice and further research.

Funding
Not stated.

Bibliographic details

PubMedID
23556044

DOI
10.4254/wjh.v5.i3.120
Original Paper URL

Indexing Status
Subject indexing assigned by CRD

MeSH
Antiviral Agents; Humans; Hepatitis C; Liver Cirrhosis

AccessionNumber
12013019353

Date bibliographic record published
24/04/2013

Date abstract record published
11/07/2013

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.